UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/126,945	07/31/1998	TOWIA ARON LIBERMANN	1488.1090000	9528

7590 05/06/2002

STERNE KESSLER GOLDSTEIN AND FOX
SUITE 600
1100 NEW YORK AVENUE N W
WASHINGTON, DC 200053934

EXAMINER
PRIEBE, SCOTT DAVID

ART UNIT	PAPER NUMBER
1632	37

DATE MAILED: 05/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/126,945	Libermann et al.
Examiner	**Art Unit**
Scott D. Priebe, Ph.D.	1632

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

THE REPLY FILED *Apr 23, 2002* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☐ In view of the early submission of the proposed reply (within two months as set forth in MPEP § 706.07 (f)), the period for reply expires on the mailing date of this Advisory Action, OR continues to run from the mailing date of the final rejection, whichever is later. In no event, however, will the statutory period for the reply expire later than SIX MONTHS from the mailing date of the final rejection.

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. X A Notice of Appeal was filed on *Apr 23, 2002*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will be entered upon the timely submission of a Notice of Appeal and Appeal Brief with requisite fees.

3. X The proposed amendment(s) will not be entered because:

   (a) X they raise new issues that would require further consideration and/or search. (See NOTE below);

   (b) X they raise the issue of new matter. (See NOTE below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: *see following pages*

4. X Applicant's reply has overcome the following rejection(s):
   The new matter rejection of claims reciting "an enhancer, a Kozak sequence, an operator", of these claims 280-287 are allowed.

5. X Newly proposed or amended claim(s) *230, 232, and 264-279* would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claim(s).

6. X The a) ☐ affidavit, b) ☐ exhibit, or c) X request for reconsideration has been considered but does NOT place the application in condition for allowance because:
   see following pages

7. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

8. X For purposes of Appeal, the status of the claim(s) is as follows (see attached written explanation, if any):
   Claim(s) allowed: *203-206, 209, 212-228, 243-246, 249, 252-256, 259, and 280-287*
   Claim(s) objected to: *159, 160, 162, 163, 165, 166, 168, 169, 183, 186, 189, 192, 230, and 232*
   Claim(s) rejected: *157, 158, 161, 167, 170-181, 184, 187, 190, 193-202, 207, 208, 210, 211, 236, 237, 239, 247, 248, 252-254, 257-259, 260-261, 264-279, and 283-284.*

9. The proposed drawing correction filed on _____ a) ☐ has b) ☐ has not been approved by the Examiner.

10. Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.

11. Other:

SCOTT D. PRIEBE, PH.D.
PRIMARY EXAMINER
ART UNIT 1632

Advisory Action (continued)

Item 3: The proposed amendment to claim 157 that the polynucleotide at least 90% identical to SEQ ID NO: 1 also encode a transcription factor has not been presented before. This new limitation in the context of pending claim 157 raises new issues of enablement, which would require a new rejection, similar at least in part to the enablement rejection of claim 180, etc.

Although the proposed amendment to claims 176, 196, 199, 207, 210, 236, 239, 247, 250, 260, 273, and 276 overcomes the new matter rejection of these claims (and their dependents), it creates a new matter issue for dependent claims 177, 197, 200, 208, 211, 237, 240, 248, 251, 261, 274, 277, as does the proposed amendment of claim 280 (and its dependent claims). Deletion of "operable" in the base claims broadens the invention of the dependent claims beyond the description where the recited transcription sequences are operably linked to a sequence encoding a fragment or all of SEQ ID NO: 2. The standing new matter rejection of claims 177, 197, 200, 208, 211, 237, 240, 248, 251, 261, 274, 277 and 280 for recitation of "an enhancer, a Kozak sequence, an operator" is withdrawn in view of Applicant's identification of support in the specification for these limitations.

The proposed amendment to claim 288 raises a new issue of new matter, similar to that applied to pending claim 264. There is no requirement in the proposed claim that the heterologous polypeptide be fused to the recited amino acid sequences.

Item 6: The various utilities described on page 13 of the response either require the polynucleotide to hybridize to a target sequence, e.g. Northern blot analysis, triplex formation, RFLP analysis, transcriptional profiling, or to encode a protein with PDEF function, e.g. gene therapy, identification of polynucleotides to which PDEF binds.

Applicant mischaracterizes page 16, lines 4-18 of the specification. Lines 4-11 describe using fragments of SEQ ID NO: 2 to induce antibodies, lines 12-18 describe other types of sequence variation, and in the context of the following paragraphs, are clearly directed biologically relevant functions of PDEF, such as in transcription, not making antibodies.

Applicant mischaracterizes Ikeda et al. This paper is directed to a method of identifying epitopes of a protein that bind a known antibody to that protein. Such a use is not taught in the instant specification, which does not disclose any known antibody to PDEF. Also, such use would be deemed non-statutory under §101 as being directed to a method of studying or further characterizing the claimed invention. As pointed out in the previous Office action, the rejection is not directed to the use of fragments of SEQ ID NO: 2 for making antibodies, it is directed to using variant polypeptides differing in up to 10% the amino acids of SEQ ID NO: 2 for this purpose. The specification does not suggest using such variants for this purpose (unless they are truncated forms of SEQ ID NO: 2).

While ETS-4 is structurally similar to PDEF, it is not at least 90% identical to SEQ ID NO: 2, nor is a functional equivalent of PDEF, i.e. it does not activate expression of PSA. Also, *Drosophila* is an insect, not a mammal; and insects do not have PSA genes or prostates. While

the structural similarity between ETS-4 and PDEF proteins suggest a common ancestry for their genes, and perhaps a similar function, at best the sequence similarity indicates amino acids which are involved in conserved structure related to the general function of these two proteins. It does not provide evidence as to those non-conserved amino acids of PDEF which must be retained for PDEF function. With respect to the teachings at page 16, lines 15-31, the specification does not disclose any other functional PDEF proteins whose amino acid sequence could be compared to SEQ ID NO: 2 in order to predict which amino acids were conserved, and thus important for structure or function, as suggested in lines 19-25. The routine methodology discussed in lines 26-31 involve testing variants that differ by a single amino acid substitution from a known functional sequence, not that differ by up to 10% of amino acids, which for SEQ ID NO: 2 would be 33 amino acids.

It is argued that the instant situation is substantially different from that in *Amgen* because the claims recite 90% identity and each case is decided on its own facts. It is not clear how the latter point shows the instant case to be substantially different. As to the 90% identity limitation, this limitation merely reduces the number of potential variants to make and test from an astronomical number to a smaller but still astronomical number. To put the situation in perspective, the number of possible amino acid sequences that are 335 amino acids long is 20^{335} or about 7×10^{435}. The number of possible amino acid sequences that are of a given %identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are only substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + ... + X^{n-1}L(L-1)(L-2)...(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)...(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, i.e. 19 alternate amino acids, L is the length of the reference sequence,, n is the maximum number of residues that can be substituted relative to the reference sequence at a given % identity. This formula is approximated by the simpler formula $N = X^nL^n/n!$, which for 90% identical to the 335 amino acid PDEF protein would be approximately 4×10^{88} possible amino acid sequences to make and then test for PDEF function. Including sequences which differ from SEQ ID NO: 2 by insertions and deletions, and combinations of insertions, deletions and substitutions would increase the number of sequences to be tested by several orders of magnitude. While limiting the scope of potential sequences to those that are at least 90% identical to a reference greatly reduces the number of potential sequences to test, it does not do so in any meaningful way. The number of possible sequences, both operative and inoperative, falls within the estimated number of atoms in the universe (10^{70} to 10^{90}). Thus, limiting the claims by the recited structural relationship to SEQ ID NO: 2 merely reduces the degree of impossibility of making and testing sequences for those which encode a protein that functions as PDEF.

Contrast the task of making and testing over 4×10^{88} with the prior art teachings described in the specification at page 16, lines 26-31 which would involve substituting one amino acid at a time, and then testing for function. For SEQ ID NO: 2, there would be almost 6.4

X 10^3 possible amino acid sequences to make and test (19 substitute amino acids per position multiplied by 335 positions for making a substitution). The number of possible sequences differing by a single amino acid form SEQ ID NO: 2 is insignificant when compared to the number of possible sequences which are at least 90% identical.

The limitation of the instant claims to polynucleotides encoding a polypeptide at least 90% identical to SEQ ID NO: 2 is a purely arbitrary limitation. It does no more to inform the skilled artisan of which specific variant sequences would be operative, i.e. have PDEF function, than were the limitation or teaching omitted. Rather than telling one skilled in the art what embodiments are operable, all this limitation does is inform one skilled in the art which potential embodiments Applicant is not claiming, and therefore need not be made and tested. The 90% identity limitation merely reduces the amount of undue experimentation required, it does not eliminate the undue experimentation required. Therefore, inclusion of the structural % identity relationships in the claim does not distinguish the instant fact situation from that reviewed in *Amgen*.

Applicant quotes *Amgen* at page 18 of the response, however this passage does not support Applicant's argument. The court held that to meet the enablement requirement for broadly claimed DNA sequences encoding a protein with a given function, the specification must disclose "how to make and use *enough sequences* to justify grant of the claims sought" (emphasis added). As in *Amgen*, the instant specification discloses only one amino acid sequence (SEQ ID NO: 2) presumed to have the required biological PDEF function.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX numbers are (703) 308-4242 or (703) 305-3014 for any type of communication. In addition, FAX numbers for a computer server system using RightFAX are also available for communications before final rejection, (703) 872-9306, and for communications after final rejection, (703) 872-9307, which will generate a return receipt. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

Any inquiry concerning administrative, procedural or formal matters relating to this application should be directed to Patent Analyst Patsy Zimmerman whose telephone number is (703) 308-8338. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe, Ph.D.
Primary Examiner
Technology Center 1600
Art Unit 1632